## REMARKS/ARGUMENTS

Claims 1-18 are pending in the application. In accordance with the restriction requirement, claims 10-12 have been canceled, without prejudice and claims 1 and 9 have been amended to restrict the claims to the diseases of cancer, angioma and angiofibroma. Applicants reserve the right to file claims to the canceled subject matter in one or more divisional applications.

Claim 1 has been amended to restrict the claims to EMMPRIN monoclonal antibodies and fragments thereof. Claim 2 has been canceled as it is now redundant with claim 1. Likewise, claims 8, 14 and 15 have been canceled in view of the amendments to claim 1.

### The Rejections Under 35 USC 112

Claim 18 was rejected under 35USC 112, first paragraph, for lack of enablement because of its reference to the UM-8D6 hybridoma that produces the CD-147 antibody. This antibody is readily available commercially from Research Diagnostics, Inc as set forth in the specification at page 18, line 20. (See the website at http://www.researchd.com/rdicdabs/cd147.htm). Accordingly, a deposit of the antibody is not required since it is available to the public commercially in the same manner as any other research reagent. See MPEP 2404.01.

Claims 1-9 and 13-18 were rejected under 35 USC 112, first paragraph because, in the Examiner's view, the specification, while being enabling for a method of treating an angiogenesis dependent disease comprising administering an anti-EMMPRIN antibody where the disease is cancer; was not enabling for any "angiogenesis-dependent disease, or any "EMMPRIN antagonist". While applicants disagree with the Examiner's view, the rejection is rendered moot by the amendment of claim 1 to recite "EMMPRIN monoclonal antibodies" and limiting the claim to cancer, in accordance with the restriction requirement.

Likewise, the 112 rejection of claim 3 based on the reference to "derivatives" of the fragments, is rendered moot by the amendment of claim 3.

Further, the 112 rejection of claim 14 and 15 relating to the "prevention" of tumor growth and metastases is rendered moot by the amendment of the claims to recite "treatment" rather than "prevention".

Finally, Applicants respectfully traverse the rejection of claim 16 on the basis that the specification does not disclose what other anti-angiogenic agent can be used other than thalidomide and anti-alphaV antibodies. At this point, one skilled in the art would have no trouble identifying other established anti-angiogenic agents by reference to the scientific literature and thus there is no need for the specification to recite a detailed list of anti-angiogenic agents. One skilled in the art would be aware of the existence of other established anti-angiogenic agent and therefore no specific disclosure is required. It is well established that what is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. See *Hybritech Inc. v Monoclonal Antibodies Inc.* 231 USPQ 81, 94 (Fed. Cir. 1986), MPEP 2163. Numerous publications are available to guide one skilled in the art in selecting other anti-angiogenic agents in addition to those recited in the specification to use in combination with the EMMPRIN monoclonal antibodies in accordance with the

invention. See for example Klagsbrun et al, "Molecular Angiogenesis, Chem. Biol., 1999, R217-224, Vol 6 of record in Applicants' Information Disclosure Statement, where a variety of known agents are described. Accordingly, the rejection should be withdrawn.

**The Rejection Under 35 USC 102 and 103**

1. Claims 1-4, 7-8, 13-15 and 18 were rejected under 35 USC 102(b) as being anticipated by WO 02/13763.

   According to the Examiner, the WO'763 patent publication discloses a method of treating tumor growth or metastasis in a patient comprising administering EMMPRIN antagonist such as an anti-EMMPRIN antibody and therefore anticipates the claimed invention. Applicants respectfully disagree that the reference anticipates the claimed invention. The claimed invention is directed to a method of treating an angiogenesis-dependent disease in a mammal in need thereof comprising administering to the mammal an EMMPRIN monoclonal antibody or fragment thereof in an amount effective to inhibit angiogenesis. The reference does not disclose or suggest treating an angiogenesis dependent disease and does not disclose any information concerning angiogenesis or how to determine an angiogenesis inhibiting amount of the antibody. The publication only contains a general reference to treating cancer with an anti-EMMPRIN antibody, but contains absolutely no data to support it. It is nothing more than speculation based on the fact that, in a prior publication, EMMPRIN expressing tumor cells had been shown to up-regulate the expression of MMPs in fibroblasts co-cultured therewith. See page 57 of WO'763. There is absolutely no data showing that inhibiting EMMPRIN can have an effect on tumor angiogenesis; or that anti-EMMPRIN antibodies or any other anti-EMMPRIN constructs can in fact inhibit tumor growth or metastases. There is no biological data using EMMPRIN antibodies and no biological data in an angiogenesis or tumor model of any kind. Therefore, the reference is completely lacking in enablement. One skilled in the art would recognize it for what it is; mere speculation. Accordingly, the rejection should be withdrawn.

2. Claims 1-2, 5, 8, 13-15 and 18 are rejected under 35 USC 102(b) as being anticipated by Zucker et al.

   This rejection should be withdrawn because the date of the publication is 2004; which is after the priority date of the present application (3/24/2003). The publication is of a grant application, that relates to a project that was started in 2000, but the actual publication used as a reference is 2004. The reference refers to studies performed by Dr. Zucker with EMMPRIN antibodies he received from the applicants of this application. Applicants are aware of this work and it was performed after the priority date of this application. Accordingly, the rejection should be withdrawn.

3. Claims 1, 2, 5-6, 9 and 13-17 were rejected under 35 USC 103(a) as being unpatentable over WO'763 in view of US Patent 6,406,693.

   The rejection over WO'763 is discussed above. The '693 patent does not add anything to the rejection since it is directed to antibodies to aminophospholipids and does not teach or suggest anything that would be relevant to anti-EMMPRIN antibodies and their use in inhibiting angiogenesis in a tumor. Because the WO'763 patent does not fairly teach or suggest the method of the invention, and the '693 patent is not relevant to EMMPRIN antibodies, the combination does not render the claimed invention obvious and the rejection should be withdrawn.

4. Claims 1, 2, 4-9 and 13-17 were rejected under 35 USC103(a) as being unpatentable over Zucker in view of the '693 patent.
Because the Zucker reference is not properly prior art, as discussed above, the combination of Zucker and the '693 patent cannot render the claimed invention obvious. Accordingly, this rejection should be withdrawn.

5. Claims 1-3 were rejected over Zucker et al in combination with Owens et al (1994). Again, because the Zucker reference is not properly prior art, as discussed above, the combination of Zucker and the Owens et al reference which is cited only for its disclosure of antibody fragments, cannot render the claimed invention obvious. Accordingly, this rejection should be withdrawn.

6. Claims 1-2, 4-8, 13-15 and 18 are rejected under 35 USC 103(a) as being unpatentable over Looksmart publication 2001 in view of Sameshima et al.

The Looksmart publication does not fairly disclose or suggest the claimed invention. Looksmart merely shows that breast cancer cells transfected with GFP-EMMPRIN produce larger tumors and that EMMPRIN can stimulate production of MMPs 1, 2 and 3. It does not teach that EMMPRIN has a direct role in angiogenesis; does not teach or suggest the use of an EMMPRIN monoclonal antibody; and does not teach or suggest that the use of EMMPRIN antibodies can inhibit angiogenesis.

These reports that cells transfected with EMMPRIN responded by producing more MMPs, are generally limited to in vitro studies, and were at best only indirect evidence suggesting EMMPRIN may be linked to angiogenesis. In many cases, the purity of EMMPRIN purified from the cancer cells was not determined. Therefore, it is very likely that other pro-angiogenic factors could have been co-purified with EMMPRIN and were accountable for the stimulation in endothelial cells observed. Unless the investigators could show that the effect of purified EMMPRIN on endothelial cells can be neutralized by anti-EMMPRIN antibodies, their findings were not confirmed. In the Looksmart publication, antisense cDNA and ribozyme constructs failed to block EMMPRIN expression and were inactive in vitro. So there is no evidence that blocking EMMPRIN would have any effect on angiogenesis.

Accordingly, the reference is at best a teaching that EMMPRIN transfected cells produce larger tumors. There is no direct evidence that EMMPRIN has a role in angiogenesis. Even if the reference could be fairly read to suggest that EMMPRIN stimulates tumor angiogenesis in vivo, which the publication does not, it would still be necessary to show with either antibody or antisense (like applicants did) that inhibiting EMMPRIN suppresses tumor angiogenesis to render the claimed invention unpatentable. The present application contains direct evidence showing:

a. Inhibiting EMMPRIN expression in tumors with anti-sense construct ("EMMPRIN antagonists") directly suppressed tumor angiogenesis in vivo, quantitatively measured by CD31 staining;

b. That inhibiting EMMPRIN led to suppression of VEGF production, a key angiogenic factor, both in vitro and in vivo. This finding is novel and clearly differentiates applicant's findings from others concerning the relationship between EMMPRIN and MMP.

Likewise, the Sameshima et al reference merely shows that EMMPRIN stimulates production of MMP-2 activators, and that anti-EMMPRIN antibodies can inhibit MT2-MMP production. This does not show that EMMPRIN has an angiogenic effect or that EMMPRIN antibodies can inhibit angiogenesis directly or that they have any effect on tumors.

Accordingly, the cited references fail to render the claimed invention obvious and the rejection should be withdrawn.

7. Claim 3 was rejected under 35 USC103(a) over Looksmart in view of Sameshima in further view of Owens et al.
Looksmart and Sameshima are discussed above. Owens et al is cited for its disclosure of antibody fragments. Because Looksmart and Sameshima do not render the claims obvious, the addition of Owens et al does not add anything to the rejection.

8. Claims 9 and 16-17 are rejected under 35 USC 103(a) as being unpatentable over Looksmart in view of Sameshima as applied to claims 1-2, 4-6, 8, 13-15 and 18 above and further in view of the '693 patent.

Looksmart and Sameshima are discussed above. The '693 patent is applied for the rejection over claim 9, which recites angioma, and claims 16 and 17 which recite the combination with other anti-angiogenic agents. Because the primary references, Looksmart and Sameshima, do not fairly teach or suggest the claimed method, the addition of the '693 patent for other anti-angiogenic agents, does not cure the deficiency in the rejection. It should therefore be withdrawn.

Applicant respectfully requests that a timely Notice of Allowance be issued in this case.

Respectfully submitted,

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